Recent expeditious growth of type 1 diabetes in the Gulf Arab Countries

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Abstract

The incidence of Type 1 Diabetes (T1D) in the Arab world, particularly, oil and gas rich Gulf Cooperative Council (GCC) countries has more than doubled in the last twenty years. Therefore, there is a dire need for careful systematic familial cohort studies, especially in high-risk populations. Several immunogenetic factors affect the pathogenesis of the disease. Genes in the human leukocyte antigen (HLA) account for the major genetic susceptibility to the disease. Triggering agents initiate disease onset by the destruction of pancreatic β-cells. The autoantibod-ies against glutamic acid decarboxylase (GADA), insulinoma antigen-2 (IA-2A), insulin (IAA), and zinc transporter-8 (ZnT-8A) comprise the most reliable biomarkers for T1D in both children and adults. Although three of the GCC countries, namely Kuwait, Saudi Arabia, and Qatar are among the top 10 countries with the high incidence rates of T1D, no proper prediction tools are applied in the region. Understanding the disease sequelae in a homogenous gene pool with high consanguinity in the GCC could help solve some of the challenges in understanding pathogenesis, as well as hasten the prevention of T1D. Arab states must incorporate T1D predictive and intervention policies on a war- 26 footing basis to minimize the burden of this serious disease.

Keywords: Type 1 diabetes; human leukocyte antigen; Arab populations; Kuwait Type 1 Diabetes Study; islet autoantibodies; prediction.

Introduction

Type 1 diabetes (T1D) is a common endocrine metabolic disease affecting children and adults across the world. It is a chronic immune-mediated disease that is characterized by insulin deficiency due to pancreatic β-cell destruction leading to hyperglycemia and is often associated with serious acute and chronic complications [1-2]. As per the natural history of T1D, the initial non-symptomatic phase of the disease is triggered upon genetically susceptible individuals. During this phase of the disease β-cell autoimmunity and breakdown of β-cell mass occurs as a result of biochemical reactions which lead to the production of autoantibodies such as glutamic acid decarboxylase (GADA), insulinoma antigen-2 (IA-2A), insulin (IAA), and zinc transporter-8 (ZnT8) which are considered as current biomarkers for β-cell autoimmunity (**Figure 1**). Symptomatic T1D often appears in childhood or adolescence, although the

symptoms can also develop much later in life [3]. A recent study stated that the life expectancy of people with T1D is still approximately 12 years less than in the general population and quality of life is reduced [4]. As causes and risk factors associated with T1D remain not fully understood, strategies for the cure and prevention developed until today have been unsuccessful. Patients with T1D are depending on a life-long insulin injection treatment [5]. Recently, however, novel interventions approach to delay the symptomatic phase by repair of the insulin gene, finding neoepitopes of HLA genes responsible for β-cell immunity, and autoantibody therapy are being tested but so far, they have been successful in animals only. These efforts might prove to be useful in the future. The Gulf Cooperation Council (GCC) is an intergovernmental organization made up of six member nations, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates (UAE). Obesity in children, sedentary mode of life, lack of vitamin D have

been proposed to be associated with the recent outbreak of T1D in the GCC [6, 7]. Although intensive glycemic control can reduce the incidence of microvascular and macrovascular complications, most people with T1D still develop these complications [8]. The GCC nations cover 2.6 million square kilometers and house approximately four-fifths of Arabian Peninsula, supporting a population of over 54 million people, of whom 26% are aged 14 years or under [9]. The total GDP of GCC nations is USD 3.464 trillion. The GCC countries have undergone rapid economic growth and urbanization, associated with reduced infant mortality and increasing life expectancy. Studies in the recent decade indicate a significant increase in occurrence of T1D in Kuwait, Saudi Arabia, and Qatar among children and adults [10, 11]. Compared with Europe and the USA the knowledge about characteristics of T1D in Arabs is incomplete [12]. In this review, we discuss various aspects of T1D in the GCC in comparison with global approaches based on the currently available literature.

Figure 1: Illustration of natural history of T1D.

Reproduced by permission with slight modification for clarity in response to "Restructuring Natural History of T1D" by Pozzilli et al (ref) that after diagnosis still there is a small portion of β-cell mass is left, initial Natural History of T1D by Eisenbarth (ref). Majority of biomarkers and islet autoantibodies develop after genetically susceptible individuals were exposed to certain triggering agents before the actual diagnosis of T1D, so called Gray Zone.

T1D continues to surge despite several therapeutic advances and its incidence continues to be highly variable among countries. In 2020, the incidence rate varied by over 500-fold, with approximately 60/100,000 in Finland [6, 12] and 0.08/100,000 in Papua New Guinea [12, 13] (**Figure 2**). It was considered a cold-area disease, common in northern Europe and America. However, this does not hold true since for instance Sardinia in the Mediterranean and Kuwait with a hot climate also have a very high incidence and Iceland with a cold climate has a low incidence. The incidence of T1D has shown steep exponential growth in several Arab countries, especially oil-rich countries; the rate of T1D in Kuwait, Saudi Arabia, and Qatar has experienced an over 100 % increase in the last 20 years [9–11, 14]. There are no published data about T1D incidence in Bahrain, Oman and UAE. Notably, all GCC countries rank among the top 10 countries with high type 2 diabetes [10]. If we presume

that T1D comprises 5-10 % of total diabetes, eventually, T1D rates in Bahrain, Oman, and UAE will not fall far from that seen in Kuwait, Saudi Arabia, and Qatar. GCC countries comprise less than 1% of the world population, however, they carry a big proportion of the burden of this severe disease (Figure 2). Recent findings from Finland, Australia, and Ireland suggest that the incidence trends have been declining or plateauing especially in children aged 4 years or under but not in older children [15, 16]. The rates are higher in boys than girls in most high-incidence countries [17, 18]. Europe has a good history of T1D registry systems in most countries developed since the late 1980s and the 1990s [19, 20]. Much of the data about the understanding of T1D have been derived from European and other western countries [19]. In the Arab world, especially in the GCC region a good infrastructure for well-planned T1D research exist, but it is not organized properly. There are excellent scattered studies with lack of follow up or systematic efforts to maintain it [21–25].
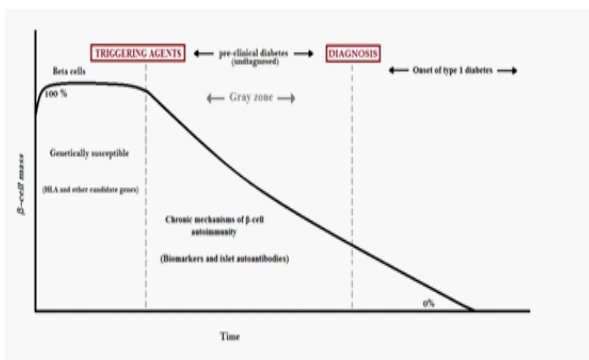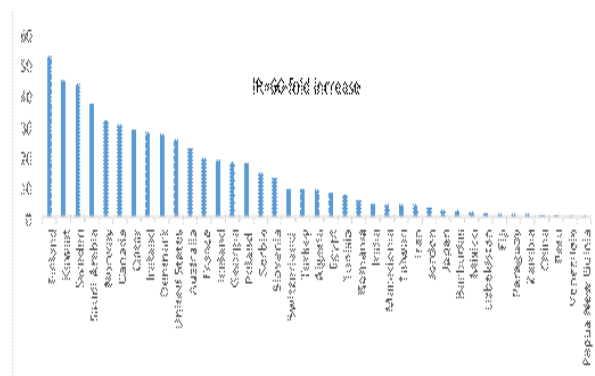

Figure 2: Incidence Rate (IR) of T1D per 100,000 population per year globally in selected countries.
The IR varies from 52.7 in Finland down to 0.8 in Papua New Guinea with more than 60-fold difference.

(**Figure 3**) illustrates the magnitude of the rate of T1D in Arab countries where data are available. This alarming increase is likely to be multifactorial. High GDP has caused drastic changes in lifestyle leading to obesity which is probably a risk factor for T1D. Other factors include lack of proper diagnostic regimens for T1D to distinguish it from so called latent autoimmune adult-onset T1D (LADA) from T2D, systematic research, proper documentation, and a T1D registry. In addition, consanguinity and endogamous marriages reported in the GCC countries are high, 23-64% making the inheritance of susceptibility genes complex [12, 26, 27]. The genetic pool of the Arab populations in the GCC is relatively homogenous with a few subgroups [13, 27]. Localizing genes and novel mutations in complex diseases have proven to be successful in such populations [12]. Hence, there is an urgent demand for data from these unique GCC populations in order to fill gaps in scientific understanding of the pathogenesis of T1D in this region.
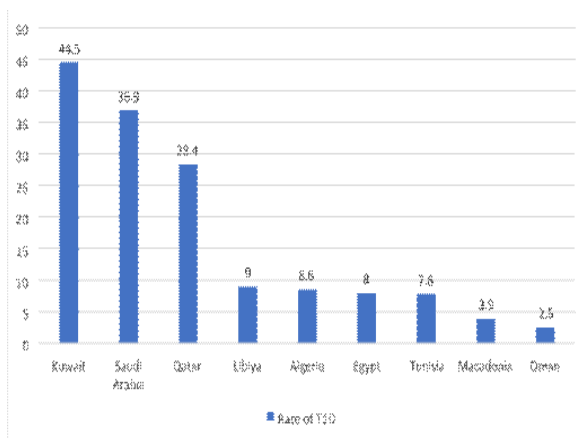
Figure 2: *Illustration of IR of T1D per 100,000 population per year in Arab Countries where data are available.*
IR of T1D in Arab Countries varies significantly with a 18-fold difference between Kuwait with 44.5 and Oman 2.5.

Genetic studies in diabetes

Genes in the HLA region explain more than 50 % of the genetic susceptibility in T1D [12]. The HLA System (the major histocompatibility complex [MHC] in humans) located on chromosome 6 is an important part of the immune system. It encodes cell surface molecules specialized to present antigenic peptides to the T-cell receptor (TCR) on T cells. HLA molecules that present antigen are divided into 3 main classes: (i) Class I that is encoded by genes at HLA-A, HLA-B, and HLA-C loci. (ii) Class II that is encoded by genes in the HLA- DR, HLA-DQ, and HLA-DP, (iii)Class III that includes complement components C2, C4, and factor B; tumor necrosis factor (TNF)-alpha, lymphotoxin, and three heat shock proteins. HLA class I and II molecules are the immunogenic antigens that are most studied in T1D in Caucasians as well as Asians. The significant associations between the HLA region and T1D diabetes were published in the 1970s [28, 29, 30, 31]. HLA has been extensively studied for the last 50 years. There is a dearth of studies on HLA among Arab populations [12, 32]. The majority of studies on HLA in T1D in Arab populations have been carried out either on selected groups of people or populations not well-specified and have concentrated on a few alleles rather than haplotypes. For example, there is no well-defined Arab HLA haplotype profile, yet [12, 25]. This is a piece of woeful news since HLA haplotypes are strongly associated with T1D, and undoubtedly any future intervention, modification of stages of the disease or cure will include HLA. Genes from the HLA region play multiple roles during an immune response and they are the first check points in its activation. Genetic polymorphisms encoding different amino acid residues in the peptide-binding pockets of HLA molecules are the main connection between HLA molecules and T1D. Moreover, the binding repertoire and affinity of peptides can be presented on T-cells [1, 33]. The strongest association with T1D is located within the HLA class II region genes that encode highly polymorphic β-chains (HLA-DRB1, DQA1, and -DQB1) (1). There are two main high-risk haplotypes "DR4-DQ8" (DR4-DQA1*03:01- DQB1*03:02) and "DR3-DQ2" (DRB1*03:01-DQA1*05:01-DQB1*02:01). Around 90% of T1D patients carry DR4-DQ8 or DR3-DQ2 and roughly 30% of patients carry the combination of both of those haplotypes (DR4-DQ8/DR3-DQ2). This group confers the highest risk of T1D development (OR = 16) [1, 34]. While there is evidence about polymorphism at the DQ locus, other HLA loci also con-

tribute to the genetic susceptibility to T1D [1, 28, 29].

HLA class I alleles are also associated with T1D [35]. In Finland with the highest incidence of T1D the absolute risk for T1D for DR4,DQ8 positive haplotypes A2,C4,B35,DR4; A3,C3,B62,DR4; A24,C7,B39,DR4; A2,C3,B62,DR4, and A2,C1,B56,DR4 was 35, 130, 166, 196, and 218/100,000, respectively. The absolute risks for DR3, DQ2 positive haplotypes A1,C7,B8,DR3, and A2,C7,B8,DR3 were 68 and 103/100,000, respectively. The absolute risk for T1D for DR4, DQ8 positive haplotypes varied significantly based on the class I gene loci. For instance, the incidence for A2,C4,B35,DR4; A3,C3,B62,DR4; A24,C7,B39,DR4; A2,C3,B62,DR4, and A2,C1,B56,DR4 was 35, 130, 166, 196, and 218/100,000 [35], when the overall incidence in the country was approximately 40/100,000. Thus, the entire HLA haplotype, not the DR or DQ loci only, is the most important factor for the genetic predisposition [1, 34]. The presence of the HLA-B*39 allele has been shown to be connected with T1D diagnosis at a young age [36]. In addition, HLA-A*02 also increases the likelihood of T1D development and is one of the most frequent class I alleles, with a frequency of > 60% in T1D patients [37, 38, 39, 40].

Genetic susceptibility: HLA patterns in different populations

Genetic susceptibility to T1D diabetes is determined by polymorphisms/ mutations in human genes [3, 34, 41, 42]. More than 50 genes are known to influence the progression of T1D [1]. Different HLA genotype patterns result in diverse rates of T1D among populations [42]. The associations of T1D with HLA class II have been shown to vary among different populations and ethnicities (Table 1) [41-47]. For example, the high-risk HLA haplotypes in Caucasian populations, DRB1*03:01-DQB1*02:01 and DRB*04:01-DQB1*03:02, were found to be low in Japan and Southeast Asia where the T1D incidence is low; instead, the susceptibility HLA haplotypes in Japanese and Korean populations were DRB1* 04:05-DQB1* 04:01 and DRB1* 09:01-DQB1*03:03[45]. Furthermore, it has been suggested that the presence of DR9 and low proportion of DR4 haplotype is an important factor in the low rate of T1D within the Japanese population [1, 45]. In fact, the variation in HLA-DR locus in HLA haplotypes in heterogenetic populations may in part explain the differences in T1D worldwide. However, this variation is not fully understood, since only limited comparisons of HLA haplotypes between populations are available [1, 52].

In African Americans, the assessment of HLA risk differs significantly from that seen in other populations; both the DRB1*07:01 and DRB1*03:03 were high-risk haplotypes when DQA1*03:01-DQB1*02:01 was included [47]. Interestingly, in African Americans, the DRB1*07:01-DQA1*02:01-DQB1*02:01g haplotype was not increased in European-derived T1D cases but was increased in African-derived cases [47]. These studies conducted in homogeneous ethnic groups and comparing HLA DR-DQ-DP haplotypes offer evidence for a link to the risk of T1D [48]. They also provide evidence that the distribution of DP alleles varies depending on the ethnic group studied [48]. (Table 1) summarizes the classification of HLA-DR in different populations and their diabetes risk level [1, 35, 41-62].

HLA genes are not transmitted randomly from parent to off-

spring, with solid linkage disequilibrium between A, C, B, DR and DQ alleles, i.e., haplotypes [1, 25, 31, 34, 38-56, 58-66]. However, in people with

T1D only a limited number of susceptibility haplotypes exist. For instance, in Finland which has the highest incidence of T1D globally, only 37 different HLA haplotypes have been identified among diabetic children who had either a parent or sibling with T1D and another 18 haplotypes in children with a first-degree relative who did not have T1D when potentially different HLA haplotypes in humans globally can be billions [67].

Table 1: *Classification of HLA haplotypes and their risk level in different populations.*

HLA-	DQ:A1	DQB1	DRB1	Susceptibility	Populations
DR2	01:02	06:02	15:01	Low risk	Almost all
DR2	01:02	05:02	16:01	Moderate Risk	Caucasians
DR2	01:03	06:01	15:02	Neutral	Caucasians, Saudi Arabia, Algeria
DR3	05:01	02:01	03:01	High Risk	Caucasians, Koreans, Bahraini Kuwaiti Egyptians
DR4	03:01	03:02	04:01	High Risk	Caucasians
DR4	03:01	03:02a	04:02	Moderate Risk	Caucasians
DR4	03:01	03:02	04:03	Neutral	Caucasians
DR4	03:01	03:02	04:04	Moderate Risk	Caucasians
DR4	03:01	03:02	04:05	High Risk	Caucasians Saudi Arabia Algerian
DR4	03:01	03:01	04:01	Neutral	Caucasians
DR4	03:01	03:03	04:01	Neutral	Caucasians
DR4*	04:05	03:03	04:01	High Risk	Japanese, Koreans
DR7	02:01	03:03	07:01	Low Risk	Caucasians
DR6	01:01	05:03	04:01	Low Risk	Caucasians
DR8*	08:02	03:01	03:02	High Risk	Japanese
DR9*	09:01	03:00	03:03	High Risk	Japanese, Koreans
DR13*	13:02	01:02	06;04	High Risk	Japanese

Configuration of HLA-DR (s) with -DQ:A1, -DQ:B1 and DR:A1 with their risk levels in different populations.
*They are only found on Asians and not in Caucasians

HLA studies in Arab populations

There are only a few HLA studies conducted in Arab countries that compare the contribution of HLA genes to the rise of T1D (Table 1) [1, 2, 35-55]. Most available studies in Arabs have not used systematic HLA research standards. They have discussed HLA associations randomly on either allele-based or haplotypes [32, 46, 55, 61-66]. Nevertheless, these studies have taken the first steps to elucidate genetic risk factors in the Arab population [44, 55, 61-66]. The hallmark of the HLA susceptibility is, however, to be considered from the haplotype point of view [3, 12, 25, 30, 31, 32, 35-37, 41-45, 447-54, 57-60]. Hamzeh et al. have analyzed 23,333 articles in 2015, of which only 30 were based on an Arab population [32]. These studies mainly discussed the genetic susceptibility of T1D related to HLA-DR or HLA-DQ alleles but not haplotype configurations. They reported that in Arabs 80% of patients with T1D are car-

riers of HLA-DR3 or DR4, typical in Caucasoid populations [32]. In addition, HLA-DR3/DR4 combination which presents the highest diabetes risk [55, 61-72] varied markedly from 13% to 75% in Arab patients with T1D.

In Arab populations (i.e., Bahrainis, Lebanese, and Tunisians) who are primarily Caucasian, DRB1*03:01-DQB1*02:01 was reported [46] (Table 1). Recently a well-planned Arab family-based study in Kuwait, Kuwaiti Autoimmune Diabetes Study (KADS) was established [12]. We have carefully collected 56 Arab families with at least a single affected member. To confirm previously reported HLA data in Arab population we have recently accomplished our 11 loci HLA typing using the state-of-the-art technology of Next Genome Sequencing; findings are being published [24, 38-40].

Other susceptibility genes for T1D

Prior to genome-wide association studies (GWAS) only five gene loci were found to be associated with T1D, HLA region, insulin (INS), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), protein tyrosine phosphatases (PTPN22), and interleukin 2 receptor alpha (IL2RA). In order to study genetic risk in T1D GWAS have revolutionized genetic studies in search of genetic risk factors. GWAS enables to investigate a genome in search of causal variants, variants that contribute to the onset of the disease but may not carry enough susceptibility for this disease in isolation. Analyses performed by The Welcome Trust Case Control Consortium (WTCCC) [76-78] and Type 1 Diabetes Genetics Consortium have revealed more than 50 genetic variants asso- ciated with T1D [42]. However, the risk of none of the non-HLA susceptibility loci had even close the risk associated with HLA. The majority of the T1D susceptibility genes identified by GWAS meta-analyses may act as modulators of an immune-related process through both antigen presentation and other modifications of the immune function [79].

Several candidate genes associated with T1D are known as modulators of β-cell apoptosis, viral infection, or islet inflammation. Some of the SNPs associated with a variation in susceptibility to T1D affect changes in gene expression; genetic variants in regulatory elements of genes can result in alteration of transcription and then gene expression. In addition, most of the identified susceptibility genes are expressed both in immune competent cells and in pancreatic β-cells, which suggests a genetically modulated dialogue between these two components of T1D [79].

Conclusion

In the three GCC countries where published data are available i.e., Kuwait, Saudi Arabia, and Qatar T1D has shown exponentially increasing incidence rates. The registration of T1D cases is, however, inadequate in the GCC countries, although it could be easily set up since these countries have free national health care systems. Many healthcare practitioners and researchers also argue that the incidence of T1D is rising sharply. The rising incidence of T1D in the GCC countries is due to several factors such as improved childhood mortality, rapid lifestyle changes, "change in nutrition" especially in the early years, changes in breastfeeding practices, environmental pollutants and toxins, immune deficiency associated with

greater hygienic standards, and low vitamin D levels which are highly prevalent in the region despite the sunshine. In people with T1D in the GCC countries, the characterization and identification of the HLA haplotypes associated with the disease and the determination of pancreatic β-cell autoantibodies as biomarkers for β-cell destruction make it possible to develop a scientifically sound prediction algorithm for T1D, but this has not developed in the GCC countries. Screening among first-degree (and second-degree) relatives of people with T1D can help to identify family members who are at risk of acquiring the disease. On the other hand, we must recognize that the penetrance of genetic predisposition is incomplete as shown by twin studies revealing that less than 50% of co-twins of an identical twin with T1D will develop the disease [80]. Thus, many people in the population transmit the genetic predisposition without having T1D themselves; thus, there are many "sporadic" cases of T1D without a close relative with T1D, but all of them have inherited T1D susceptibility genes which are necessary for the disease to develop. In addition to the lower risk of ketoacidosis at the preclinical phase, there might be a value from earlier therapeutic interventions, when some number of functioning β-cells still exists and to preserve them, while at the clinical phase after diagnosis many β-cells will be already destroyed or damaged.

There is a paucity of reports on HLA as the major genetic susceptibility predictor and on anti-islet autoantibodies in the GCC countries. A systematic study among Arab populations on HLA genetics and anti-islet autoantibody profiling is essential to add the currently missing piece in the jigsaw part of global T1D etiology.

Concluding Remarks

• T1D incidence is growing in an alarming manner in the GCC.

• T1D genotypes and phenotypes are not well characterized in the GCC.

• Misdiagnosis of LADA and T2D can happen in people who actually have T1D.

• Guidelines and procedures for the diagnosis of T1D (islet autoantibody profiling and detailed HLA typing) are needed.

• Suitable infrastructure for scientifically sound systematic scientific research on T1D is urgently needed.

• Healthcare policy makers are invited to laydown proper policies and procedures to encourage commissioning of GCC T1D consortium to utilize the research facilities and provide generously funds to establish proper GCC-T1D registry and research agenda that should be established.

Conflicts of Interest: The authors declare no conflict of interest.

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